Kinetics of Base-catalysed Condensation of 5-Methylfuran-2(3*H*)-one with 2-Hydroxybenzaldehyde

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Condensation of 5-methylfuran-2(3*H*)-one (1) with 2-hydroxybenzaldehyde (2), catalysed by triethylamine and yielding 3-acetonylcoumarin (3), was studied kinetically at 45—65°, without any solvent or with small amounts of $CHCl_3$. Two reaction intermediates were clearly detected, as well as the formation of *trans*-3-(2-hydroxybenzylidene)-5-methylfuran-2(3*H*)-one. Concentration *versus* time profiles are interpreted by a scheme involving base-catalysed condensation of (1) and (2) to form an aldol, which subsequently dehydrates to give *trans*- and *cis*-3-(2-hydroxybenzylidene)-5-methylfuran-2(3*H*)-one. The latter is finally converted into (3) by base-catalysed intramolecular acylation. The proposed kinetic scheme is also discussed on the basis of the activation parameters.

In the condensation of $\Delta^{\beta,\gamma}$-γ-lactones with carbonyl compounds, especially with aromatic aldehydes, which proceeds smoothly[1] by heating the reactants with a catalytic amount of an organic base, such as triethylamine,[1-3] $\Delta^{\beta,\gamma}$-butenolides are the chief products. With 2-hydroxybenzaldehyde, however, the reaction gives coumarin derivatives directly by internal transesterification, and in one instance only[4] an intermediate appears to have been isolated in which the phenolic hydroxy group remained unaffected.

As we are interested in the mechanism of the Thiele reaction[1] and in that of intramolecular acylation, we have studied the kinetics of the triethylamine-catalysed condensation of 5-methylfuran-2(3*H*)-one (1) and 2-hydroxybenzaldehyde (2) yielding 3-acetonylcoumarin (3), with the purpose of detecting intermediates and obtaining mechanistic information about their role.

EXPERIMENTAL

Materials.—Spectrograde solvents were used in preliminary studies and analytically pure reagents were employed throughout. 5-Methylfuran-2(3*H*)-one (1) was prepared as before.[1] Purity was checked by t.l.c. as described.[5]

trans-3-(2-*Hydroxybenzylidene*)-5-*methylfuran*-2(3H)-*one* (5). Compounds (1) (2.00 g) and (2) (2.44 g) were dissolved in cyclohexane (100 ml) and NEt_3 (0.3 ml) was added. The oily precipitate, which formed after standing at room temperature for a week was dissolved in methanol and chromatographed on silica gel with elution by 80 : 20 (v/v) light petroleum (b.p. 30—50°)–anhydrous EtOH. The collected fractions were monitored by t.l.c. on Merck GF 254 silica gel and the same eluting solvent as above. The fractions containing the pure compound were collected and extracted with $CHCl_3$. After drying and evaporation of the solvent under vacuum, the oily residue (*ca.* 5%) proved to be unstable. By this, and by a similar procedure,[6] a very pure product could never be isolated, not even after repeated preparative t.l.c., owing to the sensitivity of this substance to light. The u.v. spectrum, $\lambda_{max.}$ (MeOH) 370 and 278 nm (ε *ca.* 1.1×10^4 and 6.9×10^3 l mol^{-1} cm^{-1}) easily differentiated this substance from (3) which had $\lambda_{max.}$ (MeOH) 276 and 310 nm (ε 1.26×10^4 and 7.8×10^3 l mol^{-1} cm^{-1}). The i.r. spectrum, $\nu_{max.}$ 3 380br, 1 740 (s), 1 640 (s), and 1 600 (s) cm^{-1}, agreed with the proposed structure. The assignment of the *trans*-configuration was corroborated by the fact that this compound did not give the coumarin derivative by treatment with base, while acid-catalysed intramolecular acylation occurred.

cis-3-(2-*Hydroxybenzylidene*)-5-*methylfuran*-2(3H)-*one* (4). Compounds (1) (4.00 g) and (2) (4.88 g) and NEt_3 (0.6 ml) were reacted at 30—40 °C under the same conditions employed for the kinetic runs and the mixture was worked up as described in the kinetic procedure. By preparative t.l.c. products with R_F 0.25 and 0.54 could be isolated by extraction with $CHCl_3$ or cyclohexane, followed by neutralization, drying, and evaporation of the solvent at room temperature. The product with R_F 0.54 proved to be

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[1] (*a*) J. Thiele and F. Strauss, *Annalen*, 1901, **319**, 155; (*b*) J. Thiele, R. Tischbein, and E. Lossow, *ibid.*, p. 180.

[2] W. F. Von Ottingen, *J. Amer. Chem. Soc.*, 1930, **52**, 2024.

[3] (*a*) D. H. Marrian and P. B. Russell, *J. Chem. Soc.*, 1940, 753; (*b*) D. H. Marrian, P. B. Russell, and A. R. Todd, *Biochem. J.*, 1949, **45**, 533.

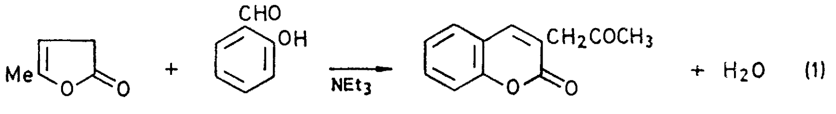
[4] R. Walter and T. C. Purcell, *Chem. and Ind.*, 1966, 2057.

[5] A. Dal Pozzo, A. Dansi, V. Mariotti, and E. Meneghini, *Boll. chim. Farm.*, 1972, **111**, 342.

[6] A. Dal Pozzo, A. Dansi, and E. Meneghini, *Boll. chim. Farm.*, 1974, **113**, 280.

identical with the *trans*-derivative (5). The intermediate with R_F 0.25 was very sensitive to light and acid and base catalysis by which it was readily converted into (3). The carbonyl and olefinic i.r. absorptions of this compound were almost identical with those of *trans*-3-(2-hydroxybenzylidene)-5-methylfuran-2(3*H*)-one, while the u.v. absorption differed mainly in the 370 nm band, which was present as a long-tailed shoulder, $\lambda_{max.}$ (MeOH) 365—370 and 279 nm (ε *ca.* 6.5×10^3 and 1.2×10^4 l mol^{-1} cm^{-1}). These properties suggested assignment of the *cis*-structure for this compound.

Kinetic Procedures.—Compounds (1) (4.00 g) and (2) (4.88 g) were mixed in thermostatted vessels under a stream of oxygen-free nitrogen. In some runs, (1) was previously dissolved in $CHCl_3$ (5 ml). Triethylamine (60—5 560 µl) was finally added to initiate the reaction. Aliquot portions of the reaction mixture were analysed after quenching by dilution with $CHCl_3$ at $-20°$. Separation of reactants, intermediates, and products was carried out by t.l.c. on Merck HF 254 silica gel and elution with 60 : 40 (v/v) chloroform–ethyl acetate, all operations being performed in the dark.



(1) (2) (3)

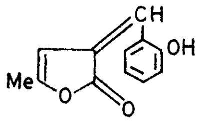
By keeping the chromatographic conditions rigorously constant and controlled, reproducibility and quantitatively satisfactory separations were attained (R_F values in parentheses): (3) (0.43); intermediate 1 (0.27); *cis*-3-(2-hydroxybenzylidene)-5-methylfuran-2(3*H*)-one (0.25), *trans*-isomer (0.54); (2) (0.60). Spots were visualized by u.v. light. Detection of (1) was not possible, because of its negligible absorption in the near-u.v. region.

Quantitative analysis was effected by the photodensitometer attachment of Zeiss PMQ II spectrophotometer, using the light remission method and the pure components as standards for the calibration, except for labile intermediate 1, for which the *cis*-3-(2-hydroxybenzylidene)-5-furan-2(3*H*)-one was employed as standard, since it was observed that its maximum absorption in the near u.v. was in the range 276—280 nm, with a molar absorptivity of *ca.* 1.1×10^4 l mol^{-1} cm^{-1}.

Alternatively spectrophotometric analysis was also carried out directly on appropriately diluted reaction mixtures. In this way, however, only the initial rate of disappearance of (2) at 255—265 nm, as well as that of formation of (3) at 270—280 nm (at longer reaction times, at which the contribution of intermediates and other products to absorption, generally low, was negligible) could be measured, by applying the principle of optical additivity to solutions.

RESULTS AND DISCUSSION

Kinetic investigation of reaction (1) in solution presented many difficulties. Hydroxylic solvents could not be used, because of transesterification of (1) with the solvent, in the presence of NEt_3 as catalyst. An inherent difficulty was afforded by one of the products: water itself hydrolysed (1) to levulinic acid under most experimental conditions at a rate greater than that of reaction (1). Consequently a 50% conversion into (3) was often the theoretical limit. In hydrocarbon solvents, such as cyclohexane, which was examined in a series of preliminary experiments, at low concentrations of (1) and (2) the reaction was too slow to be followed conveniently and secondary products resulted; an increase in concentration led to separation of intermediates and/or products. By this means, the 2-hydroxybenzylidene derivative of (1) was identified. A further complication arose because of base-catalysed isomerization [7] of (1) to 5-methylfuran-2(5*H*)-one. The product of the aldol condensation of this with (2) could be isolated in relatively high yield in cyclohexane solution when reaction was prolonged.[6] In dipolar aprotic solvents the isomerization of (1) was concurrent with reaction (1).



(4) *cis*
(5) *trans*

It was finally decided to examine the kinetics of reaction (1) in the liquid phase without a solvent or in the presence of very small amounts of chloroform, under conditions very similar to those employed by Thiele *et al.*[1] A typical concentration profile, as measured by t.l.c. followed by photodensitometric analysis of the reaction mixture is illustrated in the Figure. The decrease of concentration of (2) up to *ca.* 50% conversion can readily be observed. In the presence of chloroform, however, reaction could proceed further, particularly at higher temperatures and NEt_3 concentrations, at which 'fast' hydrolysis of (1) to levulinic acid, transformation of (1) into 5-methylfuran-2(5*H*)-one,[8] and aldol condensation of the latter [6] were possible. In the Figure the formation and decomposition of intermediate 1 and of *cis*-3-(2-hydroxybenzylidene)-5-methylfuran-2(3*H*)-one, the concentration profiles of which pass through a maximum, is evident. The *trans*-3-(2-hydroxybenzylidene) derivative of (1) was always one of the components of the reaction mixture: it appeared as a product, together with (3).

Numerical analysis of experimental data was carried out, solving simultaneous differential equations by the Runge–Kutta method: it showed that, at constant concentration of triethylamine, disappearance of (2) and formation of intermediate 1 was a second-order process [first order in both (1) and (2)], while formation of (3), as

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[7] J. Thiele, R. Tischbein, and E. Lossow, *Annalen*, 1901, **319**, 191.

Table 1

Kinetic coefficients and their standard deviations for reactions (1a—d) at various temperatures

t/°C	Initial concentrations (M) (1)	(2)	NEt$_3$	CHCl$_3$ [b]	10^3k_{1a}/mol^{-1} l s^{-1}	$10^3(k_{1a}[\mathrm{NEt_3}]^{-1})$/ mol^{-2} l^2 s^{-1}	10^2k_{1b}/s^{-1}	$10^2(k_{1b}[\mathrm{NEt_3}]^{-1})$/ mol^{-1} l s^{-1}	10^3k_{1c}/s^{-1}	$10^3(k_{1c}[\mathrm{NEt_3}]^{-1})$/ mol^{-1} l s^{-1}	10^2k_{1d}/s^{-1}	$10^2(k_{1d}[\mathrm{NEt_3}]^{-1})$ mol^{-1} l s^{-1}
45	2.12	2.12	0.380	P	0.582 ± 0.036	1.53	1.02 ± 0.43	2.68	1.28 ± 0.24	3.37	1.34 ± 0.25	3.53
45	4.85	4.85	0.380	A	0.569 ± 0.084 (0.562 ± 0.088) [a]	1.50	0.95 ± 0.20	2.50	1.19 ± 0.28	3.13	1.44 ± 0.26 (1.27 ± 0.24) [a]	3.79
54	2.99	2.99	2.99	A	8.69 ± 0.69 (9.06 ± 0.84) [a]	2.91	18.4 ± 2.8	6.15	13.8 ± 2.3	4.62	14.2 ± 3.1	4.75
54	4.53	4.53	0.814	A	2.51 ± 0.15 (2.54 ± 0.26) [a]	3.08	4.75 ± 1.1	5.84	3.91 ± 0.93	4.80	3.98 ± 1.1	4.89
54	4.75	4.75	0.518	A	1.44 ± 0.16	2.78	3.12 ± 0.22	6.02	2.44 ± 0.60	4.71	2.65 ± 0.22 (2.58 ± 0.38) [a]	5.12
54	4.85	4.85	0.380	P	1.08 ± 0.22	2.84	2.30 ± 0.15	6.05	1.85 ± 0.54	4.87	1.89 ± 0.28	4.97
54	4.98	4.98	0.180	A	0.469 ± 0.080 (0.445 ± 0.063) [a]	2.61	1.04 ± 0.09	5.78	0.873 ± 0.105	4.85	0.819 ± 0.11 (0.728 ± 0.095) [a]	4.55
54	4.98	4.98	0.089	A	0.243 ± 0.020 (0.257 ± 0.016) [a]	2.73	0.555 ± 0.068	6.24	0.457 ± 0.056	5.13	0.464 ± 0.10 (0.456 ± 0.080) [a]	5.21
65	2.12	2.12	0.380	P	2.13 ± 0.36	5.61	5.15 ± 0.82	13.5	3.09 ± 0.46	8.13	2.76 ± 0.54	7.26
65	4.75	4.75	0.518	A	3.06 ± 0.49 (3.41 ± 0.45) [a]	5.91	7.36 ± 0.89	14.2	4.32 ± 0.52	8.34	3.90 ± 0.58 (3.48 ± 0.61 [a]	7.53

[a] Spectrophotometric analysis of the reaction mixture. [b] P = present; A = absent.

well as the *cis*- and *trans*-3-(2-hydroxybenzylidene) derivatives of (1), were found to follow first-order kinetics.

$$(1) + (2) \xrightarrow[\mathrm{NEt_3}]{k_{1a}} \text{intermediate 1} \qquad (1a)$$

$$\text{intermediate 1} \xrightarrow[\mathrm{NEt_3}]{k_{1b}} (4) + H_2O \qquad (1b)$$

$$\text{intermediate 1} \xrightarrow[\mathrm{NEt_3}]{k_{1c}} (5) + H_2O \qquad (1c)$$

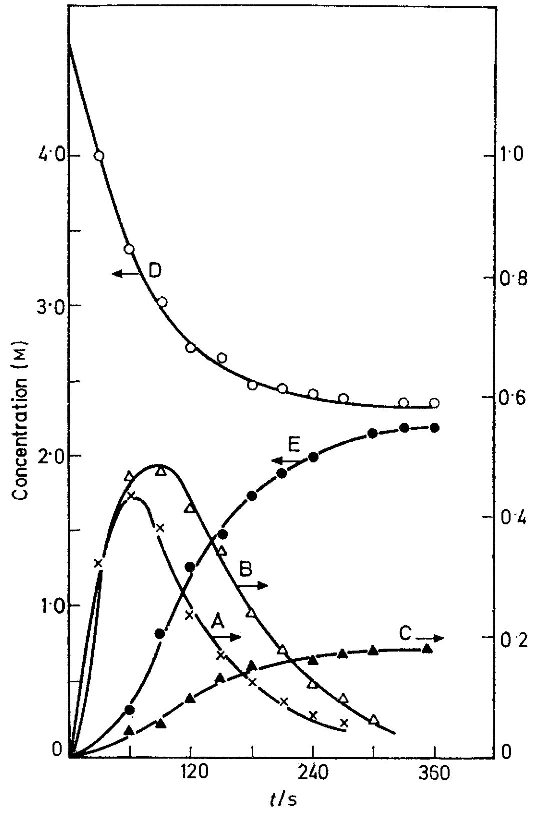
$$(4) \xrightarrow[\mathrm{NEt_3}]{k_{1d}} (3) \qquad (1d)$$

Rate coefficients k_{1a}—k_{1d} obtained by this method are reported in Table 1, and compared, whenever possible, with the same coefficients calculated by spectrophotometric analysis (k_{1a} and k_{1d}). Agreement between the two methods is fairly satisfactory. The kinetic data in Table 1 indicate that reactions (1a—d) are catalysed by triethylamine, while the presence of chloroform [accompanying (1) in some of the runs] does not seem to have exerted any appreciable effect. The influence of base catalysis on the kinetic coefficients k_{1a} and k_{1d} is shown in Table 1, where the values of $k_{1a}/[\mathrm{NEt_3}]$ and $k_{1d}/[\mathrm{NEt_3}]$ respectively, which are satisfactorily constant, are also reported.

The dehydration of intermediate 1 also appears to be base-catalysed, as is shown by the constancy of the coefficients $k_{1b}/[\mathrm{NEt_3}]$ and $k_{1c}/[\mathrm{NEt_3}]$ in Table 1. The non-catalytic rate coefficients for reactions (1b—d) have been estimated to differ by at least 1—2 orders of magnitude with respect to the catalytic rate constants. Consequently, the present treatment does not allow their evaluation.

As to the structure of intermediate 1, the parallel kinetics of reactions (1b and c), and the isolation [6] of 5-(2,α-dihydroxybenzyl)-5-methylfuran-2(5*H*)-one (which cannot be further dehydrated) in the reaction between 5-methylfuran-2(5*H*)-one and (2) suggest, as the most rational hypothesis, an aldol structure for this intermediate.

Activation parameters, calculated by the Eyring equation, for reactions (1a—d) are reported in Table 2: they were obtained by use of the catalytic constants $k_{1a-d}/[\mathrm{NEt_3}]$, respectively.



Experimental and calculated concentration profiles for the reaction of 4.75M-5-methylfuran-2(3*H*)-one (1) with 4.75M-2-hydroxybenzaldehyde (2) at 54 °C in the presence of 0.518M-triethylamine. Right-hand ordinate: A, intermediate 1 (aldol); B, (4); C, (5). Left-hand ordinate: D, (2); E, (3)

Table 2

Enthalpy [a] and entropy [a] of activation for reactions (1a—d) catalysed by NEt$_3$

	Reaction (1a)	Reaction (1b)	Reaction (1c)	Reaction (1d)
ΔH^*/kcal mol^{-1}	13.7 ±1.4	15.4 ±2.3	10.0 ±2.9	7.0 ±2.6
ΔS^*/cal mol^{-1} K^{-1}	−30.5 ±6.4	−19.3 ±4.4	−40.7 ±9.8	−45.3 ±8.9

[a] Uncertainties are probable errors, calculated by least squares, from the scattering of the Eyring plots.

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[6] L. Wolff, *Annalen*, 1885, **229**, 249.

The low accuracy of the treatment, which is reflected in the uncertainties in the kinetic parameters, stems from the experimental difficulties presented by the unusual kinetic conditions (reacting system without solvent, use of quantitative t.l.c. to measure reaction rates), and from the relatively high values of the kinetic coefficients of reactions (1b and d). As a consequence, the concentration of intermediates is often very low, and this fact, besides any analytical problem, magnifies the error, owing to the sensitivity of the rate equations for reactions (1a—d). Despite these difficulties, the activation enthalpy and entropy values are in agreement with the proposed mechanism. Reactions are controlled by entropy rather than by enthalpy effects, and this is not unrealistic in view of the steric complexity. The greater stability of the *trans*-3-(2-hydroxybenzylidene) derivative (5) of the unsaturated lactone compared with the *cis*-derivative (4) (*ca.* 5.5 kcal mol^{-1} in the transition states leading from intermediate 1 to these compounds) provides further convincing evidence in favour of mechanism (1a—d) and of the role played by an aldol as the first reaction intermediate. The low yield of the *trans*-derivative (5) of the unsaturated lactone resulting from the dehydration of the aldol is thus due to an overwhelming entropy factor in the rate coefficient. *cis*-Formation is favoured because of the planar or perpendicular carbon–carbon double bond geometry leading to the two stereoisomers. This is consistent with the observed photochemical behaviour [9] of the *trans*- and *cis*-3-(2-hydroxybenzylidene) derivatives [10] of 4,5-dihydrofuran-2(3*H*)-one.

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[9] I. R. Bellobono, L. Zanderighi, S. Omarini, B. Marcandalli, and C. Parini, *J.C.S. Perkin II*, 1975, 1529.

[10] I. R. Bellobono, B. Marcandalli, L. Zanderighi, and C. Parini, *J.C.S. Perkin II*, 1975, 1525.